PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of Frailty and Pre-Frailty among Community Dwelling Older Adults in Low and Middle Income Countries: A Systematic Review and Meta-Analysis
AUTHORS	Siriwardhana, Dhammika; Hardoon, Sarah; Rait, Greta; Weerasinghe, Manuj; Walters, Kate

VERSION 1 – REVIEW

REVIEWER	Thomas Brothers Resident physician Department of Medicine Dalhousie University Canada
REVIEW RETURNED	21-Jul-2017

GENERAL COMMENTS	I had the pleasure of reviewing this rigorous, thorough, and well-written systematic review of the published literature on frailty prevalence in low- and middle-income countries (LMICs). Following the PRISMA approach to systematic review reporting, the authors review data on prevalence of frailty and pre-frailty and include sub-analyses according to frailty assessment method, gender, and age group. They also include a meta-regression in order to identify which variables explain variability in frailty prevalence and estimates. Overall, the authors found a higher pooled prevalence of frailty in LMICs than has been previously reported for high income countries (HICs). They found high variability in estimates of frailty prevalence, which were explained largely by differences in the frailty assessment method used. They found that across studies, frailty is generally more prevalent among women than among men, and increases nonlinearly with age. Major strengths of the study include a broad search strategy and careful reporting, pre-registration of the review protocol in PROSPERO, quality assessment of included studies, and explicit acknowledgement and purposeful investigation into the influence of frailty assessment method on frailty prevalence estimates. I commend the authors for identifying and acknowledging that different approaches to the Fried frailty phenotype itself (particularly whether objectively measured or self-reported) can yield significantly different results. This is not done enough in the frailty literature, and I feel it is essential. The findings of subgroup analyses by age and gender are consistent with findings in other settings and I feel therefore increase the reliability of the pooled findings included here. There are few major weaknesses.

	I commend the authors for a well-conducted and well-reported study, and I feel this paper would make a meaningful contribution to the literature. Specific comments: (1) Methods (page 6, paragraph 2): While the age cut-off of 60 and older is reasonable (and after reviewing the literature seems even more appropriate given that many studies use that age cut-off), please describe why this cut-off was chosen in the first place.

REVIEWER	Catherine Dotchin Institute for Health and Society Newcastle University Newcastle upon Tyne UK
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	Thank you for the opportunity to review this paper on a topic that is understudied thus far. This is a very interesting and well conducted systematic review and meta-analysis of frailty prevalence in LMIC. The paper is well written, clear and easy to follow. I think it would benefit from statistical review as this is beyond the scope of my expertise. Page six I would recommend rewording line 44 to be "the largest sample and most information". It is interesting that the authors chose to focus on community dwelling individuals, when presumably there will be a higher prevalence of frailty and potentially more research focussed on hospital, clinic or nursing home based samples. They have also chosen not to include a study looking at the oldest old aged 90+, but again I think this would be of interest in its own right, even if not part of the meta analysis data. I think the comment on page 15 about frailty index limitations in populations where medical conditions are under-diagnosed is extremely pertinent and would warrant a longer discussion. Indeed, the person conducting the assessment of frailty is worthy of mention in the limitations section as it is unclear to me that many of the assessments will have been conducted by a specialist geriatrician or nurse specialist, or indeed whether gold standard frailty assessment by CGA was available at all.

REVIEWER	George Agogo Yale University, USA
REVIEW RETURNED	01-Sep-2017

GENERAL COMMENTS	1) The term pre-frailty should be defined explicitly 2) Another motivation for the use of random effects meta-regression could be due to the variation in the true effect from one study to another 3) In Table 1 column 5, why are the top three adjusted r-squared (%) negative? R-squared cannot be negative, or are these percent relative changes? 4) Figures 2 and 3 are not legible, maybe it's because of file conversion. Please check the resolution of these figures

REVIEWER	Dr Doyo G. Enki Plymouth University, UK
REVIEW RETURNED	03-Sep-2017

GENERAL COMMENTS	I enjoyed reading this work. My main comments are as follows: 1. Despite the fact that this systematic review and meta-analysis is for older adults in low and middle income countries (LMICs), there was no single study included from low income countries like Africa. In fact as mentioned by the authors, almost all the studies were from upper middle income countries, predominantly from South America. With this fact, I wonder if the resulting prevalence answers the research question of the study (and/or represents that of LMICs). 2. In the absence of consensus on the definition of 'frailty' and presence of a very large heterogeneity among the studies, how feasible is it to combine the studies? Isn't it better to report prevalence by economic status or region (as already shown to be significant factor)? 3. Based on this study, is there a statistically significant difference in prevalence of frailty between the LMICs and HICs? On page 14, the authors discussed the comparison for those aged 65 years and above; looking at the 95% confidence intervals of the prevalence, the upper confidence limit for the HICs (which is 10.9%, nearly 11%) coincides with the lower limit of the LIMCs (which is 11%). I am wondering if the prevalence is higher in HICs than the LMICs but the difference is not significant? 4. Publication bias: this problem might be related to the above comment; Eggar's test showed publication bias, but no detailed discussion given for possible reasons - could it be due to the absence of unpublished studies in the review? How was non-English studies dealt with (noting that there was no language restriction)? Funnel plot was mentioned under the Methods section, but i don't think the plot is included in the file which was sent out for review. Some minor comments: 1. would be helpful if the STATA code used in the analysis is enclosed as appendix or the relevant STATA function/package, if any, is mentioned 2. For HICs, there was a mention of 'weighted prevalence of frailty and pre-frailty' (pp 4, line 50). Was such weighting used in this study for fair comparison (if applicable)? 3. The first two forest plots were blurred on the pdf file and i was not able to comment on the figures. In addition, the figures were not labelled (i guessed to relate them to the Figures mentioned in the main body). 4. Some values of adjusted R-square are negative - not sure if these are valid numbers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Thomas Brothers
Institution and Country: Resident physician, Department of Medicine, Dalhousie University, Canada
Competing Interests: None declared.

I had the pleasure of reviewing this rigorous, thorough, and well-written systematic review of the published literature on frailty prevalence in low- and middle-income countries (LMICs). Following the PRISMA approach to systematic review reporting, the authors review data on prevalence of frailty and pre-frailty and include sub-analyses according to frailty assessment method, gender, and age group. They also include a meta-regression in order to identify which variables explain variability in frailty prevalence and estimates.

Overall, the authors found a higher pooled prevalence of frailty in LMICs than has been previously reported for high income countries (HICs). They found high variability in estimates of frailty prevalence, which were explained largely by differences in the frailty assessment method used. They found that across studies, frailty is generally more prevalent among women than among men, and increases nonlinearly with age.

Major strengths of the study include a broad search strategy and careful reporting, pre-registration of the review protocol in PROSPERO, quality assessment of included studies, and explicit acknowledgement and purposeful investigation into the influence of frailty assessment method on frailty prevalence estimates. I commend the authors for identifying and acknowledging that different approaches to the Fried frailty phenotype itself (particularly whether objectively measured or self-reported) can yield significantly different results. This is not done enough in the frailty literature, and I feel it is essential. The findings of subgroup analyses by age and gender are consistent with findings in other settings and I feel therefore increase the reliability of the pooled findings included here.

There are few major weaknesses.

I commend the authors for a well-conducted and well-reported study, and I feel this paper would make a meaningful contribution to the literature.

Response: Thank you very much for these positive comments. We are glad to hear that you enjoyed reading our manuscript.

Specific comments:
1) Methods (page 6, paragraph 2): While the age cut-off of 60 and older is reasonable (and after reviewing the literature seems even more appropriate given that many studies use that age cut-off), please describe why this cut-off was chosen in the first place.

Response: Thank you for this interesting comment. The United Nation’s agreed cut off to refer to older populations is 60 years and older (Please refer below reference). Therefore, we incorporated that cut-off to the study inclusion criteria at the outset.
(World Health Organization. Proposed working definition of an older person in Africa for the MDS Project. Geneva: World Health Organization, 2016.)
Now we have added a sentence to the methods section (page 6, para 2, line 21) outlining the reason to select this age cut-off.

Reviewer: 2
Reviewer Name: Catherine Dotchin
Institution and Country: Institute for Health and Society, Newcastle University, Newcastle upon Tyne, UK
Competing Interests: None declared

Thank you for the opportunity to review this paper on a topic that is understudied thus far. This is a very interesting and well conducted systematic review and meta-analysis of frailty prevalence in LMIC. The paper is well written, clear and easy to follow. I think it would benefit from statistical review as this is beyond the scope of my expertise.
Thank you very much for these positive comments.

1) Page six I would recommend rewording line 44 to be "the largest sample and most information".

Response: We have reworded accordingly. Now it is on page 7, para 2, line 9).

2) It is interesting that the authors chose to focus on community dwelling individuals, when presumably there will be a higher prevalence of frailty and potentially more research focussed on hospital, clinic or nursing home based samples. They have also chosen not to include a study looking at the oldest old aged 90+, but again I think this would be of interest in its own right, even if not part of the meta analysis data.

Response: We agree with both comments. We decided to focus on community dwelling older adults as many of the older adults in LMICs live in the community. And also, we believe that it is important to know the burden of frailty in this group as they live independently in the community more often. As a step for minimizing the between study variation we did not include the study with minimum recruitment age 90 in the meta-analysis. We have included a sentence summarizing the findings from this study on page 12, para 1, line 7-8.

3) I think the comment on page 15 about frailty index limitations in populations where medical conditions are under-diagnosed is extremely pertinent and would warrant a longer discussion.

Response: We agree that this is an important issue. We have added a further sentence on this point to the discussion (page 22, para 1, line 8-10).

4) Indeed, the person conducting the assessment of frailty is worthy of mention in the limitations section as it is unclear to me that many of the assessments will have been conducted by a specialist geriatrician or nurse specialist, or indeed whether gold standard frailty assessment by CGA was available at all.

Response: None of the studies have used CGA. One criteria of the quality assessment we used was “whether the outcomes measured by unbiased assessors?” (appendix B, supplementary file). Of 56 studies 40 have reported that the outcome was assessed by unbiased assessors.

Reviewer: 3
Reviewer Name: George Agogo
Institution and Country: Yale University, USA
Competing Interests: None declared

1) The term pre-frailty should be defined explicitly
Please see response to the editorial team above (comment number 2).

Response: We have addressed this in the introduction (page 4, para 3).

2) Another motivation for the use of random effects meta-regression could be due to the variation in the true effect from one study to another

Response: Thank you for highlighting this important point. We have included it on page 8, para 1, line 7-8)

3) In Table 1 column 5, why are the top three adjusted r-squared (%) negative? R-squared cannot be negative, or are these percent relative changes?

Response: The top three adjusted R square values are negative. It is possible for adjusted R square to be negative in meta-regression. For a clear explanation we have copied the relevant section of the following article; Harbord RM, Higgins JPT. Meta-regression in Stata. Stata Journal 2008;8(4):493-519. (page 500, para 1) as it is.
"The proportion of between-study variance explained by the covariates can be calculated by comparing the estimated between-study variance, τ^2, with its value when no covariates are fit, τ^2_0. Adjusted R^2 is the relative reduction in the between-study variance, $R^2_{adj} = (\tau^2_0 - \tau^2)/\tau^2_0$. It is possible for this to be negative if the covariates explain less of the heterogeneity than would be expected by chance, but the same is true for adjusted R^2 in ordinary linear regression. It may be more common in meta-regression because the number of studies is often small".

4) Figures 2 and 3 are not legible, maybe it's because of file conversion. Please check the resolution of these figures

Response: Our sincere apologies for the inconvenience caused. We have increased the resolution of the figures (300 dpi).

Reviewer: 4
Reviewer Name: Dr Doyo G. Enki
Institution and Country: Plymouth University, UK
Competing Interests: None declared

I enjoyed reading this work. My main comments are as follows:
It has been a pleasure to hear that you enjoyed reading our work. Thank you very much for the comments.

1) Despite the fact that this systematic review and meta-analysis is for older adults in low and middle income countries (LMICs), there was no single study included from low income countries like Africa. In fact as mentioned by the authors, almost all the studies were from upper middle income countries, predominantly from South America. With this fact, I wonder if the resulting prevalence answers the research question of the study (and/or represents that of LMICs).

Response: Please see response to the editorial team above (comment number 1). We acknowledged that majority of the studies in this review belongs to upper middle income countries predominantly from Latin America. However, we believe that our findings still answer the original research question by showing the limited research (two studies) available from low and lower middle income countries.

2) In the absence of consensus on the definition of 'frailty' and presence of a very large heterogeneity among the studies, how feasible is it to combine the studies? Isn't it better to report prevalence by economic status or region (as already shown to be significant factor)?

Response: Although, there is not a fully agreed definition, an overall prevalence estimate is of some use considering the population wide measures that can be taken to minimize frailty. In addition, in the sub group analysis we have presented the pooled prevalence of frailty by frailty assessment method.

We believe that this is the best way to report the prevalence given the heterogeneity of the assessment methods.

3) Based on this study, is there a statistically significant difference in prevalence of frailty between the LMICs and HICs? On page 14, the authors discussed the comparison for those aged 65 years and above; looking at the 95% confidence intervals of the prevalence, the upper confidence limit for the HICs (which is 10.9%, nearly 11%) coincides with the lower limit of the LIMCs (which is 11%). I am wondering if the prevalence is higher in HICs than the LMICs but the difference is not significant?

Response: Thank you very much for this interesting comment. Following the updated searches and our new analysis with extra studies, the confidence intervals of the LMICs ranged from 11.9 to 17.4% (page 21, para 1, line 1-2). Therefore, the new confidence interval does not overlap with the confidence interval of HICs and thus the difference is statistically significant.

4. Publication bias: this problem might be related to the above comment; Eggar's test showed publication bias, but no detailed discussion given for possible reasons - could it be due to the absence of unpublished studies in the review? How was non-English studies dealt with (noting that there was no language restriction)? Funnel plot was mentioned under the Methods section, but i don't think the plot is included in the file which was sent out for review.

Response: We have now discussed the possible reasons for funnel plot asymmetry and significant Egger's test results in detail in the discussion (page 23, para 2). Our apologies for not sending the funnel plots. We have attached the funnel plots with the revised version.
After removing the duplicate records, we found records in Arabic, Korean, Portuguese and Spanish languages. At the title and abstract screening stage we used the English translation of the title and abstract already provided in the record. In the absence of an English abstract we received the support of native Portuguese and Spanish speakers. Non English records reviewed in the full text review were either in Portuguese or Spanish. The Arabic and Korean language records were not eligible. The SciELO- Scientific Electronic Library Online covering selected collection of Brazilian scientific journals provided the English translation of the articles in Portuguese. For the others two Portuguese and Spanish native speakers (university students) helped to translate the key sections of the articles into English.

Some minor comments:

1) would be helpful if the STATA code used in the analysis is enclosed as appendix or the relevant STATA function/package, if any, is mentioned

Response: Now we have mentioned all the Stata commands we used in the methods section under the "data analysis" sub topic.

2) For HICs, there was a mention of 'weighted prevalence of frailty and pre-frailty' (pp 4, line 50). Was such weighting used in this study for fair comparison (if applicable)?

Response: We contacted first author (corresponding author) of the HICs review to get the information about the type of weighting they used. They have used simple weighting technique as follows.
weighted prevalence of frailty=∑_(i=1)^n▒n_i/N_total *Proportion frail in the i th study

Given the heterogeneity of the studies, random effect model is the best method to calculate the pooled prevalence of frailty. Therefore, we performed a supplementary analysis (page 9, para 3; page 17, para 3 and page 18 para 1) for a fair comparison of pooled frailty and pre-frailty prevalence estimates between HICs and middle income countries.

3) The first two forest plots were blurred on the pdf file and i was not able to comment on the figures. In addition, the figures were not labelled (i guessed to relate them to the Figures mentioned in the main body).

Response:We apologies for the inconvenience caused. Now we have increased the resolution of the figures (300 dpi). We have provided figure legends in the text.

4) Some values of adjusted R-square are negative - not sure if these are valid numbers.

Response: Please see our explanation provided above (reviewer 3, comment number 3).

** Additional modifications not suggested by the reviewers

Initially our search was performed in six electronic databases (MEDLINE, EMBASE and AMED, Web of Science Core Collection, CINAHL Plus, LILACS). In our updated search we also included searches of WHO Global Health Library which includes regional indexes from LMICs including LILACS. These regional indexes are African Index Medicus (AIM), LILACS (index of scientific and technical literature of Latin America and the Caribbean), IMEMR (Index Medicus for the Eastern Mediterranean Region), IMSEAR (Index Medicus for South-East Asia Region) and WPRIM (Western Pacific Region Index Medicus). When we perform the updated search we searched WHO Global Health Library from the inception to 12, September 2017.

Kappa statistics have been included to quantify the agreement between two reviewers.

Instead of mentioning simple geographic regions, The World Bank classification was used in the meta-regression.

Two sample proportion test was used to compare the prevalence of frailty and pre-frailty by sex and between LMICs and HICs.

We used the World Bank country classification issued on 1, July 2017.

A new table is included in the manuscript text (table 1) summarizing the characteristics of the studies included in the meta-analysis of frailty and pre-frailty as the table in the appendix C in the (supplementary file) is very lengthy.

Forest plots in the previous version (appendix D, E) have been replaced from a new table appendix D as forest plots are not clear enough after including extra studies from the updated search.

Order of the studies presented in the tables and forest plots has been changed.

Discussion section has included an additional point discussing the variation of approaches used to calculate Fried phenotype cut-offs.

Thank you for considering our paper for publication in your journal.
We look forward to hearing from you.

Yours sincerely,
Dhammika Deepani Siriwardhana, on behalf of all authors.

VERSION 2 – REVIEW

REVIEWER	Thomas Brothers Dalhousie University, Canada
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	I am satisfied with the author's responses to reviewer comments and feel the article is appropriate for publication.

REVIEWER	G Agogo Yale University, USA
REVIEW RETURNED	05-Dec-2017

GENERAL COMMENTS	The authors have addressed most issues that were raised by the reviewers. However, it's still not clear to me why some adjusted R-squared in Table 2 are negative. Also, the revised figures are not included in the revision files, therefore, I cannot comment on them.